

REMARKS

1. General Matters

1.1. Claims 10, 34, and 36-54 were marked withdrawn in the June 17, 2008 action. However, those claims were rejoined and allowed by the March 31, 2009 notice of allowance, and these claims were included in the present prior art rejection.

1.2. Claims 1 and 107 have been amended to recite an upper limit of six nucleobases per strand. We have amended claim 15 to recite that there are 2-5 nucleobases on each strand; 2-5 is based on P28, L2-5.

Claims 4-12, 19, 27, 28, 31, 32, 35, 49, 50, 55 and 72-78 were made directly dependent on 15.

We amended claim 16 to recite "2-4" rather than "fewer than 5" because the "2" is the minimum necessary to accommodate "CPG".

Claim 58 appeared to be equivalent in scope to 16 so we made it dependent on 3.

Claim 65, 66, 72, 100-106 remain dependent on 1. Claim 107 is independent. Claims 108-111 are new.

1.3. We thank the examiner for withdrawal of various objections and rejections (OA §1-7).

2. Prior Art Issues

The sole rejection in this case is for obviousness over Krieg WO 98/18810 (Ref. AT), Davis WO98/40100 (Ref. AU) and Shea (Ref. BT) in view of Sonehara (Ref. BV) (OA §8).

Claim 1 is presently directed to

A method of stimulating the immune system of a subject which comprises administering to the subject an immunologically effective amount of an isolated immunostimulatory molecule which comprises at least one oligonucleotide strand which comprises (1) at least one nucleotide sequence comprising a plurality of nucleotides, each nucleotide comprising a nucleobase, and thereby also comprising at least one CxG dinucleotide unit or analogue thereof, in which there are no more than seven nucleobases in each oligonucleotide strand, wherein in said analogue, (1) cytosine is

replaced with a cytosine analogue which is a pyrimidine other than thymine or uracil, and/or (2) guanine is replaced with a guanine analogue which is a purine other than adenine, and  
(2) at least one covalently incorporated lipophilic group.

Claim 107 differs from claim 1 solely by omission of the word "isolated".

The Examiner argues that Krieg and Davis teach immunostimulatory activity of oligos comprising CpG dinucleotides, but concedes that they do not teach covalent lipidation of these oligos. The Examiner believes it would have been obvious to covalently lipidate in view of Shea (see below).

However, the Examiner fails to address explicitly whether the art teaches immunostimulatory oligos in which there are no more than seven bases in each strand.

Krieg teaches that the nucleic acid sequence is "from about 8-30 bases in length". Later, Krieg teaches "preferably the immunostimulatory CpG DNA is in the range of between 8 to 30 bases", without the fuzzy word "about". The exemplary sequences are all quite a bit longer than 8 bases, see Krieg sequences 42, 43, 56-68. Moreover, Krieg declares, "Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g. Table 1, ODN 4e)". This clearly teaches against construction of "about 8" as including 6 or 7; "about" presumably only modifies "30".

Davis defines an oligonucleotide as "a polymeric form of nucleotides at least five bases in length". However, Davis adds, "preferably the CpG oligonucleotide is in the range of about 8 to 30 bases in size". The exemplary sequences 4-16 are all longer than 8 bases.

When a claimed range overlaps or lies within a range taught by prior art (and that is the only distinction), the claimed invention is prima facie obvious. MPEP 2144.05(I). That is also true if the ranges are non-overlapping, but close enough so the person of ordinary skill would expect them to have the same properties. Id. It is possible to rebut the prima facie case of

obviousness by showing (1) the criticality of the claimed range --i.e, unexpected superiority relative to the prior art range, or (2) a material "teaching away" from the claimed invention. MPEP 2144.05(III). Here, there is a clear teaching away explicitly provided by Krieg and to a lesser degree Davis.

Shea is cited merely to show that oligo-lipid conjugates are more effectively delivered to cells. The tested oligos were double stranded, and the shortest was a 15-mer<sup>1</sup>. (Krieg is said to teach that efficient cellular uptake is necessary, and thus to motivate adoption of Shea's lipidation.)

However, Krieg teaches against lipidation of the short oligos claimed herein, because Krieg teaches that oligos shorter than eight bases are not immunostimulatory. Increasing efficiency of uptake is futile if the molecule in question is not immunostimulatory. Davis expresses a preference for at least 8 bases, albeit without explanation.

WO01/97843 (IDS Ref. BB) says that the immunostimulatory nucleic acid can have any length greater than six nucleotides (P7, L2). Since we have amended claims 1 and 107 to place the upper limit at six, this is now a negative teaching.

The teachings of WO99/61056 (IDS Ref. AW) are more ambiguous. It implies that a hexanucleotide "having a sequence including at least the following formula: ("5'-X-X2-CG-X3-X4-3'...) wherein X, X2, X3 and X4 are nucleotides" might induce mucosal immunity (P3, L30) although an octanucleotide is preferred. (P8, L17). The only "exemplary" oligos in Table 1 that are smaller than octanucleotides are GTCGYT (SID 87) and TGTCGYT (SID88). However, the tested oligo was 5'TCCATGACGTTCTGACGTT-3' (SID 90) a 20-mer with two CpG's. (Ex. 1). Hence, the teaching relative to hexa- and heptanucleotides was purely speculative and hence likely to be discounted in view of the received wisdom of the art.

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<sup>1</sup> Shortest tested for inhibition of protein synthesis in Table 1, cp. Fig. 1. There were thermal denaturation studies of 11-mers in Fig. 3.

We are frankly puzzled by the Examiner's failure to expressly discuss the length issue since it was explicitly raised in section 3.3. of the last amendment. However, the examiner does argue that it would be obvious to provide the hexamer oligos of Sonehara, covalently lipidate them as taught by Shea for better uptake, and incorporate them into the compositions of Krieg and Davis. We recognize that Sonehara teaches that a CpG-containing hexamer, complexed with liposomes, elicits interferon production in mice, but the negative teaching by Krieg etc. should still have been addressed. The Examiner must consider the entire body of art, both references with positive teachings (Sonehara) and those with negative ones (Krieg; Davis; 97843).

Should the Examiner not be persuaded that a "teaching away" occurred, consideration must still be given to the dependent claims.

The method claims 58 (no more than 4 bases) and 101-104 (2, 3, 4 and 5 bases, respectively) recited oligos shorter than Sonehara's hexamer, yet those claims were rejected. Such rejection appears unjustified by any construction of the art relied on. Note that claim 15 now recites 2-5 bases.

Claims 59-64 require that the molecule (not merely the composition) comprises an epitope. Claim 59 has been amended to state that the epitope is a peptide, carbohydrate, lipid, glycopeptide or glycolipid epitope, with clear basis at P62, L32-33. Hence, even if the DNA of the cited art fortuitously provides an epitope, it would not satisfy claim 59. New claim 111 is like amended 59 but dependent on 15.

Sonehara's liposome-encapsulated oligos only induced IFN production when lipofectin was provided. Based on our Examples 28 and 29, we did not provide lipofectin in our liposomal vaccine. Since we cite Sonehara at P3, L18-21 and incorporate by reference at P140, we have basis for the limitation of new claim 108 that the molecule is immunostimulatory even in the absence of lipofectin.

Note that we judged immunostimulatory activity based on T-

cell proliferation (Ex. 30), not interferon production. New claim 109 specifies the nature of the immunostimulation.


3. Miscellaneous

In our lead embodiments, the composition provides, as separate molecules, the specific immunogen (e.g., BP1-248 of Fig. 17), and the claimed lipidated CpGoligo as an adjuvant, see compounds 1-6 of Fig. 7, and cp. claims 78-79.

Hence, we have added a claim 110, specifying that the immunostimulatory oligonucleotide molecule and the anti-cancer immunogen are different molecules, complementing claim 81. See the discussion at P18, L10-31 of our specification.

Respectfully submitted,

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